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EDITORIAL.

THE LODER JUDGMENT.

Laymen often make themselves ridiculous in discussing questions of law and jurisprudence, and perhaps we had best disarm criticism at the outset of this editorial by frankly confessing that we are neither lawyers nor judges. Of one thing concerning the Loder case, however, we are sure: it did not involve the merits of the direct-contract and serial-numbering plan, and the legality of this plan therefore remains unquestioned. Judge Holland, indeed, upheld in his charge to the jury the absolute legality of the contract plan.

It was the tripartite plan that was in question, and if it should transpire that this plan has been given a serious blow, the Loder case may even be

a blessing in disguise in forcing the N. A. R. D. to depend more generally upon direct contracts, which have both the merits of unquestioned legality and of superior efficiency. Whether the tripartite plan has, however, lost its legal prop remains to be seen.

The one issue in the case seemed to be this: Did manufacturers and jobbers refuse Loder goods by virtue of a combination or conspiracy among themselves, or did each do so upon his own individual initiative? Attorney Scott for the plaintiff sought to prove the former; Attorney Johnson for the defendants sought to prove the latter; and Judge Holland, in charging the jury, declared that "if you find there was a combination, it will be my duty to tell you that it is illegal." The decision of the jury indicated a belief in the existence of a combination or conspiracy.

Now what makes the decision somewhat confusing to the layman is this, that it is contrary to those reached in the famous and epoch-making Park* and Platt† cases. In both these it was admitted that the jobbers, the manufacturers, and the retailers had acted in concert, but it was nevertheless declared by Judge Tuley in the Platt case that "the rule invoked by [Platt's] counsel that any kind of a combination, even to keep up prices, is in restraint of trade, *does not apply to patentees or to manufacturers using trade secrets*: this appears to be well established by the authorities." Similar ground was taken in the Park decision. So far as patented or trade-marked (or even "trade-secret") preparations are concerned, the Loder decision is therefore in apparent conflict with the decisions rendered in the Platt and Park cases. So far as other classes of goods are concerned, no one of the three decisions would seem to favor any restriction in their sale through the concerted efforts of manufacturers, jobbers, or dealers.

*See BULLETIN OF PHARMACY, June, 1903, page 222.

†See BULLETIN OF PHARMACY, March, 1905, page 90.

THE NEW PHARMACOPŒIA.

A Detailed Commentary on the Eighth Revision, which Became Official September 1—Each Article is Taken Up in Alphabetical Order and the Specifications Compared with Those of the Previous Edition—The Changes Made in the Work thus Rendered Clear.

By DR. JOHN M. FRANCIS,

Chief Chemist for Parke, Davis & Co.

(Continued from the December BULLETIN.)

Fluidextractum Gelsemii.—The menstruum and process of manufacture have not been changed. This is one of the fluidextracts which is commonly adjusted to uniform strength by assay, by the manufacturing pharmacists of the United States. It is fair to presume that the Revision Committee would have adopted an assay standard for this fluid if the time had not been consumed in the investigation of the assay processes of the more important drug extracts. Gelsemium is quite a potent remedy, and it has been very difficult for some years to obtain an adequate supply of drug of good quality. It is reasonable to assume that the next revision will include an assay standard for this fluidextract.

Fluidextractum Glycyrrhizæ.—Probably none of the official fluidextracts have been subjected to so much criticism as has that of glycyrrhiza, because of its harsh taste and other objectionable qualities. The process adopted in the Eighth Revision differs very materially from that of the U. S. P., 1890, and yields a much superior fluid. Whereas the drug in No. 40 powder was formerly extracted by the use of a hydro-alcoholic menstruum; now the drug in coarse powder (No. 20) is extracted by boiling water. This decoction is reduced, the undesirable extractive is precipitated by adding to it an equal volume of alcohol, and after standing for three days the liquid is filtered, the alcohol recovered, the necessary quantity of glycerin added, and the final adjustment made by the addition of water and a sufficient amount of alcohol for the preservation of the fluidextract. In the final adjustment ammonia in sufficient quantity is added to hold the glycyrrhizin in solution.

Fluidextractum Granati.—Drug 1000 grammes; glycerin 100 Cc. Menstruum dilute alcohol. The fluidextract is prepared in the usual manner.

Fluidextractum Grindeliæ.—The menstruum is reduced from 94 per cent alcohol to a mixture of 750 Cc. of alcohol, plus 250 Cc. of water.

Fluidextractum Guaranæ.—This fluidextract is now required to contain 3.5 per cent of alkaloids when assayed by the standard process.

Fluidextractum Hydrastis.—This fluidextract must be adjusted to a content of 2 per cent of hydrastine by the appended assay process.

Fluidextractum Hyoscyami.—This fluidextract must now contain 0.075 per cent of alkaloids when assayed by the appended process. The adoption of this low standard for fluidextract of hyoscyamus seems as illogical to the writer as the adoption of the higher standard of 0.5 per cent of mydriatic alkaloids for fluidextract of belladonna root. The evidence which has accumulated in our records for the past ten years proves very conclusively that the standard of 0.1 per cent of mydriatic alkaloids is wholly practicable, and in

fact that this would be nothing more than the fair average of the alkaloidal content of commercial drug of fair quality.

It is a matter of congratulation that the "double menstruum" first of alcohol 2 parts and water 1 part, followed by dilute alcohol, is now superseded by the use of dilute alcohol throughout the operation. Just what philosophy underlay the use of two different menstrua in the preparation of a single extract was beyond our ken.

Fluidextractum Ipecacuanhæ.—Now adjusted to standard of 1.75 per cent of alkaloids by appended process. We may well afford to anticipate our comment on ipecac drug because of the importance of its use in the form of fluidextract. The new revision admits both the Rio and Carthagena ipecac, whereas former revisions recognized only the Rio. Rio ipecac has gradually become more difficult to procure, and has, particularly during the past few years, commanded an increasing price. This scarcity of the well known variety led to a search for something cheaper on the part of drug merchants and consumers, and the result was that some manufacturers listed the fluidextract of both the Rio and Carthagena ipecac. It may be also asserted that some pharmacists with singular prescience anticipated the pharmacopœial recognition of the Carthagena drug and used it either alone or mixed with Rio to produce the official fluidextract.

While some very brilliant work has been done on the chemistry of ipecac, particularly by our English colleagues, much yet remains to be accomplished before the subject can be considered as finished. If the weight of evidence points to any conclusion, however, it certainly is this, that while both varieties contain the two alkaloids, emetine and cephaeline, the former predominates in Rio and the latter in Carthagena drug. As physiological experimentation seems to have very forcibly demonstrated that emetine is less emetic than cephaeline, it follows that the Rio is better suited for expectorant compounds.

Of course we know that our committee has given due thought to this matter, and it has probably concluded that practical considerations outweigh the theoretical ones, as after all the reaction in the average patient is not acute enough to permit of definite conclusions as to the drug administered. In conclusion, it remains to be said that the physician can always get the fluidextract of genuine Rio ipecac if he wishes it.

Fluidextractum Lobeliæ.—In the U. S. P. of 1890 this drug was extracted by diluted alcohol, but now the menstruum is diluted acetic acid (275 parts acetic acid plus 725 parts water). The writer does not wish to appear hypercritical, but he must say frankly that he considers the adoption of the acetic menstrua for fluidextracts of lobelia, sanguinaria, and squill to be a grievous mistake. On the score of economy there is

nothing, or at least very little, gained, for the economy of production becomes insignificant to the individual druggist. But aside from this consideration there is the very important phase of the matter, viz., the relative efficiency of the acetic and alcoholic fluidextracts. Because of the lack of some method of assay or valuation of lobelia, it is practically impossible to arrive at assured conclusions except by clinical tests of the fluidextract, but such a change is certainly not justified by our experience with acetic fluids which can be tested or assayed with reasonable accuracy. In the case of digitalis and squill, the acetic fluids are very much inferior to the corresponding alcoholic preparations when tested on animals, and in the case of sanguinaria repeated attempts have shown very deficient extraction of the alkaloids when the official menstruum was used. We are perhaps over-hasty in our conclusions and shall continue to collect data on this subject, as there are still several years in which to watch results. Certainly the fluidextracts of squill, lobelia, and sanguinaria of the revision of 1890 were very satisfactory, and we believe that the ninth revision will discard acetic menstrea.

Fluidextractum Nux Vomica.—Little change is noted in this fluidextract except that, whereas it was formerly adjusted to 1.5 grammes total alkaloids, it must now contain 1 per cent of strychnine. This is an increase of strength, as on the average the total alkaloids of nux vomica will not yield one-half strychnine by accepted assays. Therefore, taking 1 per cent of strychnine as the basis of comparison, the corresponding fluidextract of 1890 contained a little over 0.7 per cent of strychnine. In the case of the tincture there has been a slight decrease in strength, which we approximate as being from about 0.12 to 0.10 per cent of strychnine. This discrepancy has caused more or less mental gymnastics on the part of those who compare the two standards for drug, extract, fluidextract, and tincture; the difficulty lying mainly in the fact that a new assay has been adopted, and because the tincture is prepared from the extract and not from the drug or fluidextract. It should also be remembered that, having adopted the 10 per cent tincture and the 0.1 per cent strychnine standard, it became practically necessary to force the fluidextract up to 1.0 per cent of strychnine content. The drug will on the average contain more than the minimum quantity of 1.25 per cent strychnine, but it is exceedingly difficult to extract; so that the 1 per cent strychnine standard adopted for the fluidextract does not really represent the average content of the drug, but rather the *average per cent of strychnine which can be removed from the drug* by the official process.

Before dismissing this somewhat tiresome subject the writer wishes to make an appeal for the preparation of the tincture by dilution of the fluidextract. This is wholly practicable and accurate, and in every way more convenient and cleanly than the present official process. Pharmaceutically the extract is a failure and always has been. Tedious and expensive to manufacture, it is not permanent nor does it yield a clear tincture on solution. As regards the assay process we are of the opinion that, as in the case of cinchona, we have discarded a simple, if admittedly imperfect, method for a much more complicated and perhaps less accurate one. The assay is obviously arbitrary to a certain degree. The conditions are so exacting that results obtained by different assayers will vary greatly. Tincture of nux vomica is an important and common medicament, and will undoubtedly be a favorite with the food and drug inspectors. We predict

that whenever the matter is made the basis of legal procedure the assay will be discredited by overwhelming expert evidence.

Fluidextractum Pareira.—Alcoholic strength, formerly about 67 per cent absolute by volume, has been reduced about 10 per cent. The proportion of glycerin is unchanged.

Fluidextractum Phytolacca.—Menstruum reduced in alcoholic strength, diluted alcohol now being used.

Fluidextractum Pilocarpi.—Assayed and adjusted to a standard content of 0.4 per cent of alkaloids by appended process. This standard is not by any means high, as 0.5 per cent is easily within bounds; in fact, up to within the past six or seven years, when the drug and its educts were less esteemed, *Pilocarpus jaborandi* was usually imported, and 0.75 per cent of alkaloids was considered to be a fair standard. Then for some reason the consumption of the fluidextract and the pilocarpine salts enormously increased, the sources of *Pilocarpus jaborandi* seemed to become in a measure exhausted, and the market was flooded with inferior and also spurious drug. It is no exaggeration to say that tons of leaves were sold which were not of any species of pilocarpus, nor did they contain any of the pilocarpus alkaloids. In course of time the *Pilocarpus microphyllus* found its way into the market, and, being comparatively rich in pilocarpine, has largely displaced the variety formerly best known. The Eighth Revision admits both the *Pilocarpus jaborandi* and *Pilocarpus microphyllus*. Any purchase of drug should be conditional on its meeting the pharmacopoeial assay requirement.

Data collected for some years show that of 19 lots of drug, representing about 8000 pounds purchased during 1900 to 1905, the average content of alkaloids was 0.81 per cent. Of these 19 lots, 12 assayed above 0.75 per cent, and only one assayed below 0.5 per cent of alkaloids. As further illustrating the variation of the drug available in the market from time to time, we find that, during the five years from 1895 to 1900, the average alkaloidal content of 22 lots of drug was but 0.55 per cent, only 3 samples containing 0.75 per cent or more.

Before dismissing this subject it may be interesting to recall some sensational and also questionable advertising indulged in by certain firms who attempted to arouse the suspicion of consumers of fluidextract of pilocarpus by announcing that this drug contained alkaloids antagonistic to pilocarpine. It is needless to say that there never was any basis for such an assertion, and the matter has finally been settled by physiological experimentation disproving the assertion *in toto*. The relative predominance of pilocarpine in the different species has not as yet, we believe, been thoroughly studied, and is worthy of attention.

Fluidextractum Podophylli.—Menstruum of 8 parts alcohol plus 2 parts water, unchanged. In the writer's opinion this menstruum is weak; it possesses little advantage over straight alcohol from the view-point of economy, and is certainly not so good a solvent for the resinous active principle of the drug. If it be good pharmacy to employ alcohol in the manufacture of resin of podophyllum, it is equally good pharmacy to use it as a menstruum in the fluidextract.

Fluidextractum Pruni Virginiana.—There is a notable change in the menstruum and method of preparation, and the resulting fluidextract is a great improvement over that of the preceding Pharmacopoeia. Whereas the drug was formerly moistened with a mixture of 100 Cc. glycerin and 200 Cc. of water and allowed to macerate for 48 hours for fermentative change to take place, whereby its flavor was developed, it is

now allowed to macerate for the same length of time after being saturated with a mixture of glycerin 200 Cc., alcohol 200 Cc., plus water 600 Cc. Percolation was formerly completed with alcohol 850 Cc., plus water 150 Cc., but now a mixture of alcohol 200 Cc. and water 800 Cc. is used. The most important change, however, and the one which contributes most to the improved flavor of the fluidextract, consists in slow but continuous percolation until a full yield of 1000 Cc. is obtained from 1000 grammes of drug, instead of reserving the first 800 Cc., exhausting the drug by further percolation and incorporating the condensed, weak percolate in the reserved portion. In other words, the fluidextract of wild cherry of the U. S. P. of 1890 was exceedingly harsh and astringent because of the excessive amount of tannin it contained, and it was fairly well suited to replace a fluidextract of oak-bark or kino.

Fluidextractum Quercus.—As is usual with drugs rich in tannin bodies, 100 Cc. of glycerin is used in macerating 100 Cc. of the drug. Diluted alcohol is used as a menstruum.

Fluidextractum Quillaja.—Menstruum, diluted alcohol.

Fluidextractum Rhamni Purshiana Aromaticum.—The enormous consumption of aromatic fluidextract of cascara sagrada is finally recognized and the method of preparation is a very good one, though it is wholly unnecessary to dry the mixture of drug and calcined magnesia before percolation, and an excessive quantity of alcohol is employed. We think that a great mistake was made in using compound spirit of orange as a flavor; first, because it does not blend well with the peculiar drug taste of cascara, and, second, because the public, which is the final arbiter in such matters, is accustomed to a flavor in which anise, fennel, and wintergreen predominate. So long as our committee has merely followed the example of the large manufacturers, it may well have profited by their experience. We predict that the U. S. P. "Aromatic Cascara" will be a source of loss to the druggist.

Fluidextractum Sanguinaria.—This is one of the three or four acetic fluidextracts of the new Pharmacopœia, and we think it is one of the few mistakes committed in this most splendid work. The former menstruum of 70 per cent alcohol, acidulated by 50 Cc. acetic acid for each 1000 grammes of drug, is replaced by a mixture of 275 Cc. of acetic acid plus 725 Cc. of water. Our reason for condemning this menstruum is based upon comparative results obtained in the practical manufacture of fluidextracts of not only this drug but others as well, it proving deficient in every instance. As we stated before, we may perhaps be too hasty in arriving at conclusions. See remarks under fluidextract of lobelia.

Fluidextractum Scilla.—Now an acetic-aqueous extract. Our experience so far shows very imperfect extraction and consequently a deficient fluidextract. The former menstruum was satisfactory and should have been retained.

Fluidextractum Scopolæ.—Addition. Menstruum, 800 Cc. alcohol plus water 200 Cc., as in the case of the similar drug, belladonna root. Must contain 0.5 per cent of mydriatic alkaloids by appended assay process. See remarks under belladonna root.

Fluidextractum Senegæ.—Menstruum reduced from 70 per cent alcohol to 63 per cent (approximately). The most notable change consists in substituting 30 Cc. of solution potassium hydroxide for the 50 Cc. of the volatile alkali, ammonia, formerly used to prevent gelatinization. This change is very commendable.

Fluidextractum Sennæ.—The menstruum is not changed, but the drug is first extracted with alcohol to remove the nauseous resins, which are also supposed to produce griping; the drug is then dried and percolated as usual with diluted alcohol. Both time and alcohol will be saved by placing the drug in a strong cloth, wringing or squeezing out the excess of alcohol thoroughly, and then proceeding with the percolation as usual, without the preliminary drying. The alcoholic strength of the resulting fluidextract will not be notably increased, though a 30 per cent alcoholic menstruum would have been found as satisfactory as the diluted alcohol prescribed.

Fluidextractum Staphisagria.—Menstruum, 800 Cc. alcohol plus 200 Cc. water. After the fluid has stood for some days a considerable quantity of oil will generally be found floating on the surface. As this causes annoyance in dispensing, it is advisable to chill the fluidextract and filter free from the congealed fat.

Fluidextractum Stillingia.—Remember that this fluid has an unpleasant propensity of gelatinizing, and hence should be stocked in limited quantity.

Fluidextractum Stramonii.—Menstruum, alcohol 600 Cc. plus water 300 Cc. Must assay 0.35 per cent of mydriatic alkaloids by appended process. We consider the alkaloidal standard a fair average. Of 19 lots of this drug, representing 9000 pounds, 14 assayed above 0.35 per cent and 5 assayed below. The highest content was 0.49 per cent, the lowest 0.24 per cent, and the average 0.366 per cent.

Fluidextractum Sumbul.—Menstruum, 750 Cc. alcohol plus 250 Cc. water. The characteristic substance in this drug is a resin, and the above menstruum is deficient in alcohol to properly extract it.

Fluidextractum Taraxaci.—Diluted alcohol is still employed as a menstruum, but 50 Cc. of the solution of sodium hydroxide is added to preserve the solution. The theory for the addition of the alkali is certainly very plausible, but we believe it merits confirmation. This has not, in the author's somewhat extended experience, been one of the fluids which causes trouble through lack of stability.

Fluidextractum Valeriana.—We only mention this fluidextract in order to call attention to the claim by a German investigator that the fluidextract and the tincture of valerian soon become of little therapeutic value through decomposition of the active substances. While the evidence presented is quite voluminous and certainly very discouraging, it has not been very widely accepted. This is a matter worthy of investigation, and at least warrants the advice to prepare the fluidextract and the tincture of valerian in small quantities and from fresh drug.

Fluidextractum Veratri.—The menstruum, alcohol, is stronger than necessary, as this drug can be readily exhausted by the menstruum used for fluidextract of belladonna root. It is comparatively rich in alkaloids and should be assayed and adjusted to standard. It may be well to remember that both the American and white hellebore (*V. viride* and *V. album*) are now recognized without distinction, whereas formerly only the first was admitted. The fluidextract of white hellebore constitutes but a fraction of the consumption in America. We have accumulated data which show that of 10 parcels of American hellebore the average content of alkaloid was 1.17 per cent; the highest was 1.45 per cent and the lowest 0.73 per cent.

Gelsemium.—The committee of revision was so engrossed with more important matters, that sufficient time was not available for the elaboration of an assay of either this drug or its fluidextract. As gelsemium is a very powerful drug, we append some data as to content of chloroform-soluble alkaloids estimated by weight.

Twelve samples of the cured root gave an average of 0.43 per cent of alkaloids, the highest being 0.5 per cent and the lowest 0.25 per cent.

This drug has gained quite a reputation with practitioners in that portion of the United States where it is indigenous, and it is certainly worthy of more thorough study than it has as yet received. The alkaloids are easily separated and purified, and hence would readily lend themselves to physiological experimentation.

Glandulæ Suprarenales Siccaæ.—The wonderful power of the active constituent of these glands has been recognized for only about four years, and yet it is now used the world over. We cannot recall a therapeutic agent which has so quickly and universally sprung into prominence, not even excepting antidiaphoretic serum.

As the original experiments were made with extracts of suprarenals from sheep, it was thought for some time that the organs from other animals were not available, but the demands of pharmaceutical chemists soon demonstrated that the supply from sheep was wholly inadequate, and in looking for other supplies it was quickly demonstrated that suprarenals from cattle were not only as good, but, while larger, were actually, weight for weight, more active than those of sheep. One cannot but indulge in the passing thought of how many hundreds of thousands of dollars' worth of valuable medicinal material the packing houses have converted into fertilizer. The humble cow at last is known to carry, if not the elixir of life or the philosopher's stone, something almost as marvelous in the power of restoring the (almost) dead to life.

By way of comment on the pharmacopœial specifications we would say that the description is fairly accurate. Our tests on a large number of samples, representing over 4000 pounds of desiccated glands, gave an average content of 5.5 per cent of ash. The last test given, that for identity, will not always prove satisfactory. The quantities used are too great, and hence the color reaction is not sharp enough; much better results will be obtained as follows:

Macerate 1 gramme of desiccated glands in 100 Cc. of cold water for 15 minutes; filter off a portion of the liquid, and to 10 Cc. of the clear filtrate in a test tube add $\frac{1}{2}$ Cc. of a 2 per cent solution of ferric chloride, U. S. P. An emerald-green color should almost instantly appear, which rapidly fades and is slowly replaced by a reddish or claret color; this persists for some time and after several hours turns to a dingy or muddy green color.

Several factors may interfere with the sharpness of the above reaction, the most notable being too great concentration of the aqueous extract. Hence too great a quantity of material, too prolonged maceration, or the use of warm water should be avoided. The sharpness of the reaction is materially interfered with by too much iron in solution, and excessive acid causes the colors to appear much more slowly and the tints are not so sharp. We consider the succeeding red color to be much more reliable than the green alone, as we have found by experimentation that suprarenal matter, decomposed by manipulation so as to be wholly devoid of its characteristic physiological activity, would still give the green-

color test with solutions of the iron salts, but the red or claret color did not appear. We may say in conclusion that the above test is not absolute; it is merely an identity test, and does not serve to distinguish good material from inferior. Furthermore, experimentation shows that quite a number of artificial catechol derivatives will give this color reaction with solutions of iron.

While discussing this subject one may be led to inquire as to the production of a synthetic adrenalin or active suprarenal body. We think we may assure our readers that all evidence points to the probability of the cow and the sheep continuing to be the source of supplies for some time to come. The problem is certainly an attractive one, and it has engrossed the attention of a number of the most skilful chemists at home and abroad. A number of patents have been taken out, but no synthetic substance has yet been able to substitute the natural one, and as time passes the practical solution of the problem seems less and less probable, though of course it cannot be declared an impossibility.

Glandulæ Thyroidæ Siccaæ.—Thyroid glands of the sheep. Possibly the first thought which presents itself is, if the cow serves as a source of suprarenal glands, why not also use bovine thyroids? We can answer this only by saying that after many years of practical experience the consensus of opinion seems to be that thyroid glands from the cow are inferior. Our estimation of ash from many samples of the desiccated glands shows an average of 4.3 per cent.

The identity test given in the Pharmacopœia depends upon the peculiar fact that these glands contain iodine. The flesh is destroyed by incineration and fusion, and the iodine, being released in solution by the acid and nitrite, is absorbed by the chloroform, to which it imparts its characteristic color. The proportion of iodine in these glands varies greatly, being in some instances reduced to a mere trace; as the quantity at best is very small this official test can be greatly improved by fusing 5 grammes of the desiccated glands instead of 1 gramme; and no matter whether 1 or 5 grammes are used, reduce the chloroform from 5 Cc. as prescribed to 2 Cc. or less. Two or three minims of highly colored chloroform can be readily distinguished in the bottom of a clean test-tube.

A very evident misprint is found in the copy of the Pharmacopœia in the author's possession, as in the test for detecting iodine in thyroid glands it is directed that 2 grammes of sodium nitrite acidified with strong nitric acid be used. Evidently 0.2 gramme of sodium nitrite was intended here, as 2 grammes is excessive and interferes very materially with the test. At any rate 0.2 gramme is wholly sufficient to accomplish the desired result.

As in case of the suprarenals, the test for thyroids is only one of identity and will not serve to distinguish fresh, active glands from the inferior. The results of research, published by Baumann and others seven or eight years ago, certainly establish the conclusion that the percentage of iodine is not an index of physiological activity.

It is well to remember that both desiccated suprarenals and thyroids, like all fleshy material, will develop a characteristic odor in time, and this is greatly expedited by heat and moisture. Consequently the pharmacist should use some precaution to keep his stock in good condition, and furthermore he should not overstock. Such material can always be had fresh within ten days or two weeks.

(To be continued.)